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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/899,381	07/02/2001	Glenda C. Delenstarr	10010760-1	3033

7590 09/26/2003

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/899,381	DELENSTARR ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. This application contains claims 1-12 and 24-27 drawn to an invention nonelected with traverse in Paper No. 11, received 02 December 2002. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

2. The specification is objected to as documents have been improperly incorporated by reference; see, e.g., paragraph 36. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Applicant has provided numerous bibliographic citations throughout the specification, such citations do not "identify with detailed particularity what specific material it incorporates and clearly indicate where that material is to be found in eh various documents." Accordingly, said documents have not been properly incorporated by reference.

3. The disclosure is objected to because of the following informalities: In paragraph 14, fine 1, there appears the phrase "[a]t some prior to..."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute

even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

5. For convenience, claim 13, the sole independent claim under consideration on the merits, is reproduced below.

13. (Original) A method of detecting the presence of an analyte nucleic acid in a sample, said method comprising:

(a) providing a nucleic acid array comprising:
  (i) at least one hybridization feature to which said analyte nucleic acid specifically binds under stringent hybridization conditions; and
  (ii) at least one background feature;
(b) contacting said nucleic acid array with said sample under stringent hybridization conditions;
(c) detecting a hybridization signal from said hybridization feature and background signal from said background feature;
(d) subtracting said background signal from said hybridization signal to obtain a background corrected hybridization signal; and
(e) relating said background corrected hybridization signal to the presence of said analyte target nucleic acid in said sample to detect the presence of said analyte target nucleic acid in said sample.

The definitions of "hybridization feature" and "background feature" are reproduced below.

[63] A "hybridization feature" is defined as a structure comprised of a plurality of hybridization probes that selectively hybridize to a detectably labeled target nucleotide sequence, wherein the target may be labeled prior to or after hybridization, preferably prior to hybridization, as defined above. In a preferred embodiment, a hybridization feature contains 3.1×10^6 to 6.3×10^7 hybridization probes, preferably 1.6×10^7 to 4.7×10^7, more preferably 2.8×10^7 to 3.5×10^7 hybridization probes.

[64] A "background feature" is defined as a structure comprised of a plurality of background probes that do not selectively hybridize to the target nucleotide sequence, as defined above. A background feature is a feature that provides a signal during a hybridization assay that is made up of three components: (a) a feature substrate background component; (b) a probe background component; and (c) a non-specific binding component. In a preferred embodiment, a background feature is a region of an array that contains background probes covalently bound to the array-surface. In a preferred embodiment, a background feature contains 3.1×10^6 to 6.3×10^7 background probes, preferably 1.6×10^7 to 4.7×10^7, more preferably 2.8×10^7 to 3.5×10^7 background probes.

A review of the specification has found the following examples.

Example 1

[128] Empirically observed inactive probes

Example 2

[129] Utilization of empirically observed inactive probes

Example 3

[130] Probes forming highly stable intramolecular structures

Example 4

[131] Short Probes

Example 5

[132] Chemically Modified Probes

Example 6

[133] Use of background features in background-correcting the signal of hybridization features

Example 7

[134] Use of background features in determinations of LLD

This example demonstrates the impact that different background-correction methods have on the calculation of Lower Limit of Detection (LLD). As demonstrated in

Example 8

[135] Identification of Background Features Suitable for 60-Mer Arrays

6. Of the above-identified examples, only examples 6, 7 and 8 are considered applicable to the claimed invention.

7. As presently worded, the method of claim 13 requires the subtraction of a "background signal" from a "hybridization signal." The method does not require that the hybridization probe or the analyte (target nucleic acid) be detectably labeled. It stands to reason, therefore, that the "corrected hybridization signal" would be zero and no analyte nucleic acid would be detected even if present. In support of this position, it is noted that claim 14 requires that a labeling step be performed. Given that a dependent claim must further limit an independent claim, no such labeling needs to be used in the method of claim 13. It is also noted that claim 14 does not specify just what it is that is being labeled by the labeling step.

8. While hybridization is performed under "stringent conditions," there is no recitation that unbound analyte nucleic acid and/or unincorporated label are removed from the assay system. A review of the specification, including the examples, fail to find an enabling disclosure in such "such full, clear, concise, and exact" terms that one of skill in the art would be able to practice the full scope of the claimed invention, including embodiments where unincorporated label is retained and ultimately detected. Franzen et al. (US Publication No. 2003/-143581 A1) states:

> [0011] The currently available detection strategy for DNA hybridization on surface arrays employs fluorescently labeled oligonucleotides and a reader consisting of a fluorescence microscope. Lipschutz et al., (1999) Nature Genet 21: 20-24. Currently, the most compact array is the GeneChip.TM. array that consists of 65,536 single stranded DNA sequences on a chip. Lipschutz et al., (1999) Nat. Genet. Sup. 21: 20-24; Harrington et al., (2000) Curr. Opin. Microbiol. 3: 285-91. Hybridization is probed by determining the fluorescence intensity at the location of each individual sequence of the DNA array. In the ideal case only complementary DNA in solution will hybridize and produce a fluorescent signal. However,

non-specific binding and single/multi-base mismatches can provide a significant background signal. Although the background intensity is often weaker for non-specific interactions, the interpretation of the hybridization assay in terms of sequence becomes much more difficult. Consequently, statistical analysis is often required to extract the appropriate sequence information.

While the claimed method is to be practiced under "stringent" conditions, said conditions have been interpreted as allowing for multiple mismatches. The instant specification is silent on just what statistical analysis needs to be performed when trying to detect a signal resulting from multiple mismatches.

Schembri et al. (US Pub. No. 2003/0113724 A1) disclose additional problems confronting the use of nucleic acid arrays.

> [0008] A problem in the DNA microarray hybridization art is sporadic poor hybridization assay performance characterized by low-intensity or missing features on the microarray substrate, high backgrounds, and visually "blotchy" substrates. For microarrays containing DNA on adsorbed polymer substrate surfaces, this problem has been observed using conventional hybridization conditions, such as using a solution comprising 20.times. SSC (3.0 M NaCl, 300 mM Sodium Citrate (pH 7.0), 10% SDS) at high hybridization temperature of about 65.degree. C. and within conventional hybridization times of about 6 hrs. to about 24 hours.

As noted above, the specification is silent as to how 'sporadic poor hybridization performance," as well as "missing features on the microarray substrate, high backgrounds, and visually 'blotchy' substrates" is to be overcome. As presently worded, there need be but a single background feature present. Clearly, one data point in an otherwise splotchy field will not produce a background signal representative of all areas and in turn, result in accurate results for all hybridization features that have specifically bound to an analyte nucleic acid.

9. As noted above, the specification contains language whereby prior art documents have been improperly incorporated by reference. As a consequence, the specification is essentially

silent as to how nucleic acid arrays are to be produced and used, much less overcome art-recognized difficulties. As presently worded, the claims fairly encompass hybridization features of virtually any number, density, length, and nucleotide composition. Said claims also fairly encompass the analysis of nucleic acid samples that can be highly heterogeneous. At page 5 of the response of 12 May 2003, hereinafter the response, applicant acknowledges the concern and reasserts in the absence of factual underpinning that the claimed invention is fully enabled.

10. Of the 8 examples provided, none of said examples, including Examples 6-8, address these issues.

11. At page 5 of the response applicant directs attention to paragraphs 64 and 88-95 as providing "extensive generic description of he background features." Attention is also directed to where 28 different probes are provided. A review of paragraphs 64 and 88-95 fails to find any exemplification of where 28 different probes were used.

12. Page 5, last paragraph, of the response directs attention to paragraph 59 of the specification, in that it provides "description of representative nucleic acids that may be employed as probes." A review of said paragraph 59, however, produces but a definition of "a 'hybridization probe.'"

At page 6 of the response it is asserted that "[t]he specification also provides a full description of the sample and hybridization conditions that are employed in the subject assays." Attention is directed to paragraphs 78 and 110-113. A review of paragraph 78 find exemplary conditions that are used to characterize the expression "stringent conditions." The conditions set forth there in have not been interpreted as being performed in the context of the claimed method. A review of paragraphs 110-113 finds general teachings of how hybridization reactions are

conducted generally, along with reference to Sambrook, Fritsch & Maniatis, *Molecular Cloning: A Laboratory Manual*, Second Edition (1989). The response, including the cited paragraphs, do not teach how one is to overcome the art-recognized issues of array synthesis and hybridization reactions such as those noted by Schleifer et al., and Carrico. In support of this position as it relates to the manufacture and use of oligonucleotide arrays, US Patent 6,077,674 (Schleifer et al.) addresses certain highly problematic areas:

> While in situ synthesis is a very flexible means for producing DNA arrays, the fidelity or percentage of full-length oligonucleotides synthesized within a feature on the array is less than 100 percent. An ideal array will have only full-length oligonucleotides attached to each feature. The ideal array promotes accuracy in hybridization experiments or assays or target biological materials. If the fidelity of an in situ generated array is less than 100 percent, it typically has non full-length oligonucleotides within a feature that usually consists of shorter lengths of the correct sequence, and to a lesser degree, incorrect sequences. Typical DNA coupling efficiencies are around 97 to 99 percent for the standard phosphoramidite chemistry. For oligonucleotides that are 25 nucleotides in length, these efficiencies result in only 46 to 77 percent full-length oligonucleotides contained within a feature (0.97^{25} to 0.99^{25}). This loss of fidelity can cause chemical noise in hybridization conditions. The loss of fidelity can also lead to difficulty in interpreting the data.
>
> Photolithography is a method used by Affymetrix in California to produce in situ arrays using procedures that are similar to those used in the semi-conductor industry. In procedure described by Fodor et al. from Affymetrix U.S. Pat. No. 5,405,783, a photo-deprotection step is used where the protecting group on the phosphoramidite is removed by exposing a photosensitive protecting group to light. Four photo masks are used to create patterns to de-protect areas of the substrate and then a nucleotide is added to these regions. This technique requires four masks for each layer of nucleotides. While this technique allows for the production of high-density oligonucleotide arrays, it is less efficient than traditional phosphoramidite synthesis chemistry. With efficiencies of about 90 to 95 percent, the percentage of full-length oligonucleotides within a feature is further reduced to about 9 to 27 percent for oligonucleotides that are 25 nucleotides long (0.90^{25} to 0.95^{25}).

Carrico, (US Patent 5,200,313) similarly identifies problematic aspects of hybridization reactions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

13. In view of the innumerable art-recognized difficulties, the failure of the specification to teach one of skill in the art how to overcome these issues, and the unpredictability I the art, the burden of enabling the full scope of the claims is unfairly shifted from applicant to the public. Indeed, the reference that applicant directs one toward (Sambrook et al.) was published in 1989, and as such is wholly silent as to how issues recognized in the art subsequent to publication. Claims 13-23 remain rejected under 35 USC 112, first paragraph, as not being enabled by the disclosure.

Conclusion

14. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 6,077,673 (Chenchik et al.) discloses using positive and negative controls for determining background levels on arrays; see columns 8-9.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

16. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

18. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

19. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS